REMARKS

Status of the Claims

Claims 18-38 are currently pending, while the Office withdrew claims 20-34 from consideration. Thus, claims 18, 19, and 35-38 are under examination at this time. Applicants maintain the request for rejoinder of withdrawn claims 32 and 33, in accordance with 37 C.F.R. § 1.141 and M.P.E.P. § 821.04, upon allowance of claims 18 and 19, from which claims 32 and 33 depend. (See Remarks filed November 19, 2002, at page 3.)

Applicants' Summary of the Interview of July 16, 2003

Applicants thank Examiner Meller for the helpful interview with Applicants' representatives at which the 35 U.S.C. § 112 and 102 rejections and the Hanada publication was discussed. Applicants' arguments and evidence mentioned at the interview is presented below, in Attachments A-C, or in the accompanying Information Disclosure Statement.

Rejection of Claims 18, 19, and 35-38 under 35 U.S.C. § 112, first paragraph

The Office newly rejects claims 18, 19, and 35-38 under 35 U.S.C. § 112, asserting that they are not enabled.

Applicants traverse this rejection and submit that the Office does not present a *prima facie* case of nonenablement in accordance with the substantial evidence standard of *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Instead, the Office

[illegible] and all inhibitors of thrombin, sugars,

sugar alcohols, amino acids, etc. to see if they could perform the disclosed use." (Office Action of May 6, 2003, at page 3.) The Federal Circuit has specifically pointed out that such a broad, sweeping conclusory statement is not sufficient to support a *prima facie* case. *In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002). Instead, under *Zurko* and *Lee*, the Office's conclusions must be supported by fact-based reasoning or substantial evidence.

Nevertheless, Applicants herein provide evidence to show that claims 18, 19, and 35-38 are enabled. First, the class of "noncovalently binding inhibitors of thrombin activity" is relatively small. These compounds comprise those that directly inhibit the activity of thrombin by binding to thrombin noncovalently at low to moderate affinity and in which their addition does not significantly decrease the activity in relation to fibrinogen in a coagulation test. (See the specification at page 6, first full paragraph, to page 7, line 4.) As thrombin is a serine protease utilizing an arginine or lysine in its active site, the class includes arginine-derived or benzamidine-based inhibitors that are known to bind with high affinity to the thrombin active site. (Specification at page 6, first full paragraph.) Representative examples are discussed in the attached article by Stürzebecher et al. in the Information Disclosure Statement. These examples are amino acid derivatives that contain benzamidine or a basic-substituted benzene ring on the side-chain. (Stürzebecher et al., page 496, final paragraph.) In addition, because thrombin is a medically important protein, several small molecule therapeutic thrombin inhibitors have been developed and are safe for therapeutic use as indicated in the accompanying Information Disclosure Statement, references clinical trials on a small set

of therapeutically acceptable small-molecule direct thrombin inhibitors. (See Hauptmann at page 752, column 2, discussing the benzamidine-based inhibitor NAPAP and others, citing publications describing the development and clinical testing of these inhibitors prior to Applicants' filing date.) Thus, several of direct thrombin inhibitors, in themselves, were known to be therapeutically suitable at the time this application was filed. Thus, one of ordinary skill in the art could reasonably predict that such agents would not compromise the therapeutic suitability of the instant thrombin preparations because they are already known to be safe for human administration. Further, a coagulation test is a simple, routine procedure that involves determining whether a blood sample coagulates if a given solution is added to it. Systems for performing such tests are also commercially available. There is no undue experimentation in testing a claimed composition in such a coagulation test.

Second, the optional components of the solution recited in claim 19, (e.g. sugars, amino acids, sugar alcohols, and salts of carboxylic acids or hydrocarboxylic acids) are all commonly used buffer ingredients in therapeutic blood protein solutions. These agents, for example, are frequently added simply as preservatives to enhance the shelf-life of the overall protein composition, or to protect the protein from exposure to high temperatures. (See the Specification at page 1, final paragraph, to page 2, end of third full paragraph.) The Information Disclosure Statement accompanying this Reply includes four United States patents disclosing the use of salt, amino acid, sugar, and sugar alcohol additives in therapeutic, liquid blood protein preparations. U.S. Patent

generally useful preservatives added to blood protein solutions, for example to enhance

their stability to heat. The patent gives many examples of amino acids, sugars, and sugar alcohols that can be used with a variety of blood proteins. (See col. 3, lines 45-50, and the further discussion at col. 4.) U.S. Patents 4,579,735, 4,623,717, and 4,876,241 contain similar disclosures. All four of these patents show that those in the art believe these classes of compounds to be generally useful additives, and also show that many different species within those classes are routinely used in protein solutions. Moreover, the Office does not present any evidence or reasoning to suggest that any of these agents would detract from the usefulness or therapeutic suitability of the instant, claimed preparations, or that they would change the key properties of the claimed preparations in any way. Thus, no undue experimentation is needed to select one or a combination of the additives recited in claim 19.

Finally, many factors must be considered when judging whether or not a particular type of experimentation is "undue." The predictability and the level of guidance provided in the specification are only two of several factors to consider. Some of the other factors include the level of skill of those working in the art, the type of experiments that are considered routine to those in the art, the guidance available in the prior art, and the "state" or maturity of the art in general. *See* M.P.E.P. § 2164.01; *In re Wands*, 8 U.S.P.Q. 1400, 1404 (Fed. Cir. 1988). Further, a composition may be enabled even though it requires a considerable amount of experimentation to make or use, if that experimentation is routine or is guided by the art. *See* M.P.E.P. §§ 2164.01 and 2164.06; *In re Wands*, 8 U.S.P.Q. at 1404 (citing *In re Anastadt*, 190 U.S.P.Q. 214

The articles and patents submitted herewith in the Information Disclosure Statement show that the art of preparing liquid protein solutions is relatively mature and that those in the art are familiar with the sugar, sugar alcohol, amino acid, and carboxylic acid additives recited in claim 19. The articles provided herewith also show that the available class of "noncovalently binding inhibitors of thrombin activity" is relatively small and that it includes compounds that are known to be "suitable for therapeutic purposes" in themselves.

In addition, the types of tests required to show that the preparations are suitable for their intended use or are sufficiently stable according to claim 37 are simple to perform and are standard procedures in the pharmaceutical arts. For example, one can perform a simple protease assay after 12 months of storage to determine if the thrombin meets the activity requirements of claim 37. One may perform a straightforward animal toxicity or clearance screen against a control thrombin preparation to verify the therapeutic suitability of the claimed preparations.

In summary, the Office does not present a *prima facie* case of non-enablement. Further, the Office does not consider that the art of making and using blood protein preparations is relatively mature and that the experimental procedures required to make and use the claimed preparations are straightforward. Accordingly, Applicants request the withdrawal of this rejection.

Rejection of Claims 18 and 35-37 under 35 U.S.C. § 102(b): Hanada et al.

The Off

this rejection, and provide the following additional remarks.

Applicants first note that a *prima facie* case of anticipation is only established if the reference expressly or inherently teaches every element or limitation of the claim, including any functional limitations. M.P.E.P. § 2131. Claim 18 includes two ingredients: "thrombin" and a "noncovalently binding inhibitor of thrombin activity," and also contains a functional limitation that must be considered: "wherein the thrombin preparation," meaning the overall claimed preparation with both of these ingredients included, "is ***suitable for therapeutic purposes***." The purpose of the functional language is to limit the scope of this claim to preparations that, in their entirety with all ingredients added, are physiologically tolerable and may, for example, be directly administered to a patient. Therefore, claim 18 does not cover every solution containing both thrombin and a "noncovalently binding inhibitor of thrombin activity" but only covers a discrete subset of such solutions that are "suitable for therapeutic purposes." The solution of Hanada is not such a solution.

Hanada's composition is not in a therapeutically suitable form because it includes agents called trialkylphosphates. According to evidence that Applicants have already placed on record, these agents are intended to disrupt biological membranes and are skin irritants. (See Exhibits A-C of the Amendment filed November 19, 2002, resubmitted herewith, and page 6 of that Amendment.) Therefore, they are potentially harmful to human tissues. Further supporting that Hanada's composition is not "suitable for therapeutic use" is Hanada's disclosure that the trialkylphosphates are removed before any therapeutically suitable thrombin preparation is ultimate

Applicants further reiterate that the only way Hanada's solution could, *arguendo*, anticipate Applicants' claims is under the high standard of inherency, because Hanada does not teach that the trialkylphosphate-containing intermediate is suitable for therapeutic purposes. Thus, the Office must establish that the Hanada intermediate ***necessarily*** functions in accordance with claims 18 and 35-37. As the Federal Circuit has explained, "[i]nherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268-9, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991.) To support an anticipation rejection based on inherency, the Office must provide factual and technical grounds establishing that the Hanada solution, despite the presence of the trialkylphosphates, is ***necessarily*** therapeutically suitable. *See In re Oelrich*, 666 F.2d 578,581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981); *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *see also* M.P.E.P. § 2131.01 (III). Because the Office has not provided any such showing, it has not established a *prima facie* case of anticipation, and Applicants request the withdrawal of this rejection.

Rejection of Claims 18 and 35-37 under 35 U.S.C. § 102(b): Allary or Lorne

The Office also rejects claims 18 and 35-37 as allegedly anticipated by the English-language abstracts of Allary et al. ("Allary"; *Ann. Pharmaceutiques Francaises*, 48(3): 129-135 (1990)) or Lorne et al. ("Lorne"; *Rev. Fr. Transfus. Hemotiol.*, 32: 391-

Like Hanada, neither Lorne nor Allary teaches a preparation comprising both thrombin and a "noncovalently binding inhibitor of thrombin activity" such that the overall composition with both ingredients is "suitable for therapeutic purposes." Instead, both Allary and Lorne, two papers from the same research group, teach the use of a benzamidine inhibitor placed onto a solid Spherodex® affinity column matrix. This affinity column is used to prepare a pure thrombin solution. Lorne specifically teaches that after the chromatography procedure, the thrombin eluate must be further purified by ultrafiltration or dialysis before it can be used therapeutically. Lorne at page 399, final full paragraph may be translated as follows, referring to the modes of elution presented in Table 1 on page 398:

> Whatever mode of elution is chosen, the final recuperation of the thrombin obtained by chromatography must obligatorily be treated by a preliminary dialysis or ultrafiltration in 1 M NaCl to dissociate the complex formed with the elution agent. Afterwards, the salt can be eliminated by dialysis against water and 10 g/L glucose in order to obtain the protein in good condition for lyophilization.

(Applicants are willing to provide certified translations of Allary and Lorne if the Office so requires.)

Thus, there is no evidence that the eluates from either Lorne or Allary's columns are "suitable for therapeutic purposes" according to claim 18. Nor is there evidence that these eluates could inherently and necessarily produce the preparation of claim 18. For example, they could contain unsuitable run-off from the Spherodex® columns and there is no evidence that the eluates are suitably sterilized.

necessary functional limitations of claim 18. Thus, this is not a *prima facie* case of

anticipation. The burden is on the Office to support this rejection with the necessary reasoning and evidence according to the standards of *Zurko* and *Lee*, *supra*. For these reasons, Applicants request the withdrawal of this rejection.

Rejections under 35 U.S.C. § 103(a)

1. Rejection of Claim 38 over Hanada and Claims 18, 19, and 35-38 over Hanada, Brezniak and Altshuler

The Office also rejects claim 38 over Hanada under § 103(a), and rejects claims 18, 19, and 35-38 under § 103(a) over Hanada in combination with Brezniak et al. ("Brezniak"; *Blood Coagulation and Fibrinolysis*, 5: 847-8 (1994)) and Altshuler et al. ("Altshuler"; U.S. Patent No. 4,363,319). (See Amendment filed November 19, 2002, at pages 6-8.) Applicants continue to traverse these rejections.

In order for a combination of references to render a claim obvious, there must be both a suggestion or motivation to modify the references or to combine their teachings and a reasonable expectation of success in performing the combination. M.P.E.P. § 2142. Moreover, the motivation to combine the references and the reasonable expectation of success must both be found in the references themselves or in the knowledge generally available to one of ordinary skill in the art; not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2142. Finally, the mere fact that the references ***can*** be combined or modified does not itself render the combination obvious. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Instead, the modifi

Applicants reiterate that there is no motivation in Hanada alone, or in combination with Brezniak and Altshuler, to add a noncovalently binding inhibitor of thrombin activity to any ***therapeutically suitable*** thrombin solution. Hanada itself does not suggest adding an inhibitor of thrombin activity to that therapeutic solution, but only teaches adding it as part of trialkylphosphate treatment and removing the components of the trialkylphosphate treatment ***before*** preparing a pure thrombin solution. (Hanada at col. 4, lines 13-37, and col. 5, lines 25-50.) Thus, Hanada, in fact, teaches away from adding such an inhibitor to a therapeutic thrombin solution. Neither Brezniak or Altshuler address this issue. Because there is no motivation to combine these references, Applicants request the withdrawal of this rejection.

2. Rejection of Claims 18, 19, and 35-38 over Hanada, Lorne, Allary, Brezniak, and Altshuler

The Office also rejects claims 18, 19, and 35-38 over combinations of all five of the above-cited publications, with either Hanada or Lorne and Allary taken as the primary reference. Applications traverse both of these rejections.

Not only does Hanada fail to teach adding a "noncovalently binding inhibitor of thrombin activity" to a therapeutic thrombin solution, but so do Lorne and Allary. As stated above, Lorne teaches specifically that once its column chromatography method is complete, it is obligatory to completely remove all ingredients of the chromatography buffers from the thrombin so as to obtain it in pure form. Only then may the thrombin be used in a therapeutically suitable manner. (Lorne at page 399, last full paragraph.)

Thus, taken as a whole, Hanada, Lorne and Allary teach away from using thrombin inhibitors such as benzamidine. Collectively, these references only show the use of benzamidine in a protein purification chromatography scheme, and specifically show or state that a thrombin inhibitor such as benzamidine must be removed before any therapeutically suitable composition of thrombin could be made. (Hanada at Example 1, column 5; Lorne at page 399, last full paragraph.) Again, neither Brezniak nor Altshuler addresses this issue at all. Thus, there is no motivation to combine these five publications, and Applicants respectfully request the withdrawal of these rejections.

In view of the foregoing remarks, Applicants respectfully request the reconsideration and reexamination of this application, the timely allowance of claims 18, 19, and 35-38, and the rejoinder of claims 32 and 33.

Please grant any extensions of time required to enter this response. If there are any fees required to enter this amendment that are not found herewith or otherwise entered, please charge those fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: September 8, 2003

By: _____
Elizabeth A. Doherty
Reg. No. 50,894

FINNEGAN
HENDERSON
FARABOW

Attachments: **Exhibits A-C**

NTP CHEMICAL REPOSITORY
TRIBUTYL PHOSPHATE

-IDENTIFIERS
==========

*CATALOG ID NUMBER: 002085

*CAS NUMBER: 126-73-8

*BASE CHEMICAL NAME: TRIBUTYLPHOSPHATE

*PRIMARY NAME: TRIBUTYL PHOSPHATE

*CHEMICAL FORMULA: C12H27O4P

*STRUCTURAL FORMULA: (CH3CH2CH2CH2O)3PO

*WLN: Not available

*SYNONYMS:
BUTYL PHOSPHATE, TRI-
CELLUPHOS 4
TBP
PHOSPHORIC ACID, TRIBUTYL ESTER
TRI-N-BUTYL PHOSPHATE

-PHYSICAL CHEMICAL DATA
======================

*PHYSICAL DESCRIPTION: LITERATURE: Colorless to pale yellow liquid
REPOSITORY: Clear, pale-yellow liquid

*MOLECULAR WEIGHT: 266.36

*SPECIFIC GRAVITY: 0.9727 @ 25/4 C [017]

*DENSITY: Not available

*MP (DEG C): <-80 C [031,062,421]

*BP (DEG C): 289 C [017,031]

*SOLUBILITIES:
WATER : <1 mg/mL @ 20.5 C (RAD)

DMSO : >=100 mg/mL @ 20.5 C (RAD)

95% ETHANOL : >=100 mg/mL @ 20.5 C (RAD)

METHANOL : Not available

OTHER SOLVENTS:
Ether: Soluble [017]

Benzene: Soluble [017]
Common organic solvents: Miscible [421]

*VOLATILITY:
Vapor pressure: 13.7 mm Hg @ 20 C [058]
Vapor density : 9.20 [042]

*FLAMMABILITY(FLASH POINT):
This chemical has a flash point of 146 C (295 F) [042,062,421]. It is combustible. Fires involving this material can be controlled with a dry chemical, carbon dioxide or Halon extinguisher. The autoignition temperature of this compound is >482 C (>900 F) [058].

*UEL: Not available
LEL: Not available

*REACTIVITY:
This compound is incompatible with strong oxidizing agents and strong bases [269]. It will attack some forms of plastics and rubber [102].

*STABILITY:
This material hydrolyzes slowly under wet alkaline conditions [058]. Solutions of this chemical in water, DMSO, 95% ethanol or acetone should be stable for 24 hours under normal lab conditions (RAD).

*OTHER PHYSICAL DATA:
Refractive index: 1.4224 @ 25 C
Viscosity: 4.5 centipoise @ 25 C
Boiling point: 160-162 C @ 15 mm Hg [017]; 177-178 C @ 27 mm Hg [031]
Boiling point: 180-183 C @ 22 mm Hg [058]

-TOXICITY

*NIOSH REGISTRY NUMBER: TC7700000

*TOXICITY: **(abbreviations)**

typ. dose	mode	specie	amount	units	other
LD50	orl	rat	3000	mg/kg	
LD50	ipr	rat	251	mg/kg	
LDLo	ivn	rat	100	mg/kg	
LD50	orl	mus	1189	mg/kg	
LC50	ihl	mus	1300	mg/m3	
LDLo	ipr	mus	63	mg/kg	
LDLo	scu	mus	3	gm/kg	
LCLo	ihl	cat	24510	mg/m3/5H	

*AQTX/TLM96: Not available

*SAX TOXICITY EVALUATION:
THR: A skin and eye irritant. HIGH via intravenous and intraperitoneal routes. MODERATE via oral route. It has effects on the central nervous system in humans. It is irritating to mucous [illegible]

test	lowest dose	test	lowest dose
Not available			

*TERATOGENICITY:
  Reproductive Effects Data:
    TDLo: orl-rat 12600 mg/kg (63D male)

*STANDARDS, REGULATIONS & RECOMMENDATIONS:
  OSHA: Federal Register (1/19/89) and 29 CFR 1910.1000 Subpart Z
        Transitional Limit: PEL-TWA 5 mg/m3 [610]
        Final Limit: PEL-TWA 0.2 ppm [610]
  ACGIH: TLV-TWA 0.2 ppm [015,413,421,610]
  NIOSH Criteria Document: None
  NFPA Hazard Rating: Health (H): 2
                      Flammability (F): 1
                      Reactivity (R): 0
  H2: Materials hazardous to health, but areas may be entered freely with
      full-faced mask self-contained breathing apparatus which provides
      eye protection (see NFPA for details).
  F1: Materials that must be preheated before ignition can occur (see NFPA
      for details).
  R0: Materials which are normally stable even under fire exposure conditions
      and which are not reactive with water (see NFPA for details).

*OTHER TOXICITY DATA:
  Skin and Eye Irritation:
    skn-rbt 10 mg/24H open
    eye-rbt 97 mg
  Status: "NIOSH Manual of Analytical Methods" Vol 3
          "NIOSH Manual of Analytical Methods" to be revised by June, 1985
          Reported in EPA TSCA Inventory, 1983
          Meets criteria for proposed OSHA Medical Records Rule

-OTHER DATA (Regulatory)
 ========================

*PROPER SHIPPING NAME (IATA): Not restricted

*UN/ID NUMBER:

*HAZARD CLASS: SUBSIDIARY RISK: PACKING GROUP:

*LABELS REQUIRED:

*PACKAGING: PASSENGER: PKG. INSTR.:   MAXIMUM QUANTITY:
            CARGO   : PKG. INSTR.:   MAXIMUM QUANTITY:

*SPECIAL PROVISIONS:

*USES:
  Plasticizer for cellulose esters; lacquers; plastic and vinyl resins; heat
  exchange medium; solvent extraction of metal ions from solution of reactor
  products; solvent for nitrocellulose and cellulose acetate; pigment grinding
  assistant; antifoam agent; and dielectric.

*ACUTE/CHRONIC HAZARDS:
This compound is a mild **CHOLINESTERASE INHIBITOR** [151]. It is a mucous membrane irritant [031]. It is a skin irritant and is narcotic [421]. When heated to decomposition it emits toxic fumes of POx [042].

*MINIMUM PROTECTIVE CLOTHING:
If Tyvek-type disposable protective clothing is not worn during handling of this chemical, wear disposable Tyvek-type sleeves taped to your gloves.

*RECOMMENDED GLOVE MATERIALS:
Recommended Glove Type For Use With Neat (Undiluted) Chemical:
Recommendations based on permeation test results are made for handling the neat (undiluted) chemical. If this chemical makes direct contact with your glove, or if a tear, puncture or hole develops, replace them at once.

Suggested Glove Type(s) (RAD): No information available

*RECOMMENDED RESPIRATOR:
Where the neat test chemical is weighed and diluted, wear a NIOSH-approved half face respirator equipped with an organic vapor/acid gas cartridge (specific for organic vapors, HCl, acid gas and SO2) with a dust/mist filter.

*OTHER: Not available

*STORAGE PRECAUTIONS:
You should store this chemical under ambient temperatures, and keep it away from oxidizing materials.

*SPILLS AND LEAKAGE:
If you spill this chemical, FIRST REMOVE ALL SOURCES OF IGNITION. Then, use absorbent paper to pick up all liquid spill material. Your contaminated clothing and absorbent paper should be sealed in a vapor-tight plastic bag for eventual disposal. Solvent wash all contaminated surfaces with 60-70% ethanol followed by washing with a soap and water solution. Do not reenter the contaminated area until the Safety Officer (or other responsible person) has verified that the area has been properly cleaned.

*DISPOSAL AND WASTE TREATMENT: Not available

-EMERGENCY PROCEDURES
==========

*SKIN CONTACT:
IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently wash all affected skin areas thoroughly with soap and water.
IMMEDIATELY call a hospital or poison control center even if no symptoms (such as redness or irritation) develop.
IMMEDIATELY transport the victim to a hospital for treatment after washing the affected areas.

[illegible] symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop.
Provide proper respiratory protection to rescuers entering an unknown

atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used; if not available, use a level of protection greater than or equal to that advised under Respirator Recommendation.

*EYE CONTACT:

First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center.

Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician.

IMMEDIATELY transport the victim after flushing eyes to a hospital even if no symptoms (such as redness or irritation) develop.

*INGESTION:

DO NOT INDUCE VOMITING. If the victim is conscious and not convulsing, administer a slurry of activated charcoal in water and simultaneously call a hospital or poison control center. IMMEDIATELY transport the victim to a hospital.

If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY transport the victim to a hospital.

*SYMPTOMS:

Symptoms of acute exposure to this compound may include headaches, tremors, drowsiness, convulsions, hypnosis and anesthesia [042]. It can cause weakness, dyspnea, coma and pulmonary edema [151]. It can also cause nausea [058]. It is irritating to the mucous membranes [031]. It is also irritating to the skin [421].

-SOURCES
=======

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Please send queries, comments, and suggestions to: **ntpwm@niehs.nih.gov**

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